

# Medical Therapy Update in Crohn's Disease

Andrew DuPont<sup>1,2</sup> and Atilla Ertan<sup>1,2\*</sup>

<sup>1</sup>Ertan Digestive Disease Center- Inflammatory Bowel Disease Center, USA

<sup>2</sup>University of Texas Health Science Center Gastroenterology, Hepatology and Nutrition Division and Memorial Hermann Hospital, USA

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**\*Corresponding author:** Atilla Ertan, The UTH-MHH Ertan Digestive Disease Center and Gastroenterology Center of Excellence, 6400 Fannin, Suite 1400, Houston, Texas 77030, USA, Tel: 713-704-5928, 713-704-3450; Fax: 713-704-3485; E-mail: [atilla.ertan@uth.tmc.edu](mailto:atilla.ertan@uth.tmc.edu)

## Editorial

Crohn's disease (CD) is a chronic inflammatory bowel disease that is suspected to result from a dysregulated immune system in genetically predisposed individuals, which can lead to abdominal pain, diarrhea, malnutrition and extra- intestinal manifestations. Intestinal inflammation and subsequent symptoms tend to recur over time and can lead to other complications, such as fistulas, abscesses, and strictures. CD is a chronic progressive condition, with most patients developing penetrating and/or stricturing complications over time.

Previously, only limited treatment options existed; however, over the past 30 years progress has been made regarding management of CD. The goals of treatment include: healing inflammation (mucosal healing; and ideally transmural healing), preventing recurrent inflammation and symptoms, reducing and eliminating the use of steroids, decreasing hospitalizations and surgical intervention, preventing complications, improving quality of the life and alternate the natural course of CD.

Initially, treatment for CD consisted of corticosteroids, other anti- inflammatory medications (5-aminosalicylates), and often times surgery. Corticosteroids can reduce inflammation anywhere in the body, but it is not effective for long-term treatment of patients with CD and is associated with many significant side effects.

Other treatments have been developed to directly suppress the immune response, rather than only treating inflammation, which is the result of the abnormal immune response. These medications include immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate) and more recently biologic agents (infliximab, adalimumab, certolizumab, and natalizumab). It is generally recommended patients with CD be treated with the combination of immunomodulator therapy and a biologic agent to increase the likelihood of steroid-free induction and long-term remission [1,2]. According to our experience and general consensus, patients with CD who should be considered for early biologic therapy include: young age at disease onset, steroid-refractory disease, deep ulceration or fistulizing disease, multiple antibodies to intestinal flora, perianal disease, and extensive disease in the upper small intestine.

Infliximab (Remicade) was the first biologic agent approved for the management of CD. It is an antibody that binds to the tumor necrosis factor (TNF), which blocks its activity and leads to decreased inflammation. Infliximab consists of a partial mouse antibody that is given as an intravenous infusion over a period of at least 2-3 hours. It is initially infused 3 times over a 6 week period and if there is significant improvement, every 2 months for maintenance therapy [1,2]. Infliximab is generally well tolerated; however, rarely it can be associated with infusion reactions. Because TNF is an important component of the immune system, infliximab and other biologic medications affect the body's ability to fight infections, so patients should be checked for tuberculosis and hepatitis B prior to starting these medications. It is also important to avoid live vaccines while taking these medications [1].

Adalimumab (Humira) is another anti-TNF agent similar to infliximab, which decreases inflammation by blocking TNF; however, adalimumab consists of a fully humanized anti-TNF antibody, and it is administered by subcutaneous injection, rather than an infusion. After the loading dose is given in 2 doses over a 2 week period, it is administered every other week for maintenance therapy [3]. It is also generally well- tolerated with the most common side effect being skin reactions at the site of the injection that may cause itching, redness, and swelling. Adalimumab has been shown to have similar effectiveness and safety when compared to infliximab for inducing and maintaining remission in patients with CD. It has also been shown to be effective for some patients who have failed or cannot tolerate infliximab [1].

Certolizumab pegol (Cimzia) is a pegylated humanized antibody fragment that also acts by blocking the activity of TNF. It was approved for use in the US in 2008 for the treatment of moderate to severe CD in patients who do not respond sufficiently or adequately to standard medical therapy. Certolizumab is a subcutaneous injection, similar to adalimumab, and is given twice over a 2 week period then once a month for maintenance therapy. It has been shown to be effective in inducing and maintaining remission in Crohn's disease with similar adverse events as seen with Infliximab and Adalimumab [4]. It has also been shown to be effective for some patients who have failed or cannot tolerate infliximab.

Natalizumab (Tysabri) is a humanized monoclonal antibody to alpha-4 integrin, which acts by affecting lymphocytic trafficking. It has been approved for moderate to severe CD that has not responded to other treatment. It is given as an IV infusion over 1 hour once a month [5]. Natalizumab should not be used with other immunosuppressive medications. Because it has been associated with a rare, but serious, brain infection (progressive multifocal leukoencephalopathy, PML), it is only available through a special restricted distribution program. Vedolizumab, a newer biologic agent, also affects lymphocytic trafficking. According to well- designed studies, this agent induces a gut-selective blockade of alpha-4 beta-7 integrin which appears to eliminate the risk of PML with similar efficacy when compared to other commercially available biologics for the treatment of patients with CD [6,7]. Vedolizumab is expected to be approved by the FDA for the treatment of patients with CD within 2014 and appears to be another promising new biologic agent.

These agents have never been directly compared head-to-head, and the decision to start one or another should be individualized [1]. Biologic therapy with these commercially available agents leads to clinical remission in approximately 30% and clinical response in 50% of patients with active CD [1-8]. Among those CD patients who respond initially to anti-TNF agents, up to 30-40% will lose response over time [1-8]. Therefore, extensive investigations with newer agents with different mechanisms are needed and are in progress (Table 1).

Interleukin (IL)-12 and IL-23 have been shown to play an important role in T helper cell and innate lymphocyte cell differentiation and expansion. Ustekinumab (Stelara), a fully humanized IgG1 monoclonal antibody to the p40 subunit shared by IL-12 and IL-23, has emerged as a very promising treatment option, especially in complicated CD patients who are refractory to other biologics [9,10]. Other potential agents currently in development are shown in Table 1, which includes newer oral agents [11-15]. Fecal microbiota transplantation has also been reported to be successful in small case series and case reports for the treatment of CD; however, more research is needed in this area.

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**Table 1:** New agents in development for the treatment of Crohn's Disease.

Name	Major Effect	Product
Etolizumab	Antibody to beta-7 of integrins	Humanized GI specific MCA
Ustekinumab	Anti-IL- 12/23 P40	Human IgG1 MCA
Tocilizumab	Anti-IL-6	Humanized MCA
Secukinumab	Anti-IL-17	Humanized MCA
<b>Tofacitinib*</b>	Janus kinase inhibitor	Immunomodulator
<b>Fingolimod*</b>	Sphingosine 1PR1 modulator	Lymphocyte receptor agonist
<b>HMPL-004*</b>	Herbal mixture	Anti-inflammatory
<b>GSK1605786*</b>	CCR9 antagonist	GI specific immunomodulator

\*Oral Agents

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